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Review

Basic and clinical aspects of gastrointestinal pain

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ABSTRACT

The gastrointestinal (GI) tract is a system of organs within multicellular animals which facilitates the ingestion, digestion, and absorption of food with subsequent defecation of waste. A complex arrangement of nerves and ancillary cells contributes to the sensorimotor apparatus required to subserve such essential functions that are with the exception of the extreme upper and lower ends of the GI tract normally subconscious. However, it also has the potential to provide conscious awareness of injury. Although this function can be protective, when dysregulated, particularly on a chronic basis, the same system can lead to considerable morbidity. The anatomical and molecular basis of gastrointestinal nociception, conditions associated with chronic unexplained visceral pain, and developments in treatment are presented in this review.

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1. Introduction

The gastrointestinal (GI) tract is a system of organs within multicellular animals which facilitates the ingestion, digestion, and absorption of food with subsequent defecation of waste. A complex arrangement of nerves and ancillary cells contributes to the sensorimotor apparatus required to subserve such essential functions that are with the exception of the extreme upper and lower ends of the GI tract normally subconscious. However, it also has the potential to provide conscious awareness of injury. From a teleologic perspective such an arrangement may have been advantageous, and in certain current circumstances continues to be protective. However, when dysregulated, particularly on a chronic basis, the same system can lead to considerable morbidity.

1.1. Scope

The review is limited to areas that are of most interest from basic science or clinical standpoints, particularly where the former informs the latter and where there are important differences from somatic pain. As the title suggests, where possible, the review will focus on human research, however, it necessarily draws much from observations in experimental animals. It also only considers the luminal component of the digestive system and not the conditions affecting solid ancillary organs, e.g. chronic pancreatitis. Of special note, the review has attempted to pull away from the sole discussion of the currently fashionable and repetitively reviewed [10,11,127,164] area of visceral hypersensitivity. The review is ordered on the basis of a progression from basic to clinical with the following structure:

1. Anatomical basis of GI nociception (spinal, vagal pathways and the enteric nervous system).
2. Molecular basis of GI nociception (peripheral and central signalling and sensitisation).
3. Modulatory influences on GI nociception (descending neural, autonomic and hypothalamo–pituitary axis).

Abbreviations: ACC, anterior cingulated cortex; ASIC, acid-sensing ion channel; ATP, adenosine triphosphate; ANS, autonomic nervous system; CGRP, calcitonin gene-related peptide; CCK, cholecystokinin; CRH, corticotrophin-releasing hormone; CS, central sensitisation; ENS, enteric nervous system; 5HT, 5-hydroxytrypamine; FGID, functional gastrointestinal disorders; GI, gastrointestinal; GINMD, gastrointestinal neuromuscular disease; GCPR, G-protein-coupled receptor; HAP, hypothalamo–pituitary axis; IB4, isolectin-B4; IGLE, intraganglionic laminar ending; NGF, nerve growth factor; LC, locus cereleus; NDMA, N-methyl-D-aspartate; NK, neurokinin; PAG, peri-aquaductal grey; PG, prostaglandin; PAR, protease-activated receptor; SP, substance-P; SNS, sacral nerve stimulation; SST, somatostain; TTX, tetrodotoxin; TRP, transient receptor potential; VH, visceral hypersensitivity; VGSC, voltage-gated sodium channel.

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4. Clinical syndromes characterised by chronic unexplained GI pain:
   a. Clinical overview and importance.
   b. Applied pathophysiology.
5. Treatment of chronic GI pain.

2. The anatomical basis of GI nociception

2.1. General organisation

Important differences exist between the organisation of the somatic nervous system and that of the viscera reflecting the complex embryology of the GI tract. These variations represent the functional fusion of migrating neural crest cells that form intrinsic ganglionic plexuses and vagal neurons [47] with extrinsic nerves that also develop from the neural crest, but which migrate in response to similar cues as blood vessels in the mesentery [51]. In contrast to somatic nociception, the situation in the gut is therefore complicated by the presence of two extrinsic innervations (vagal and spinal), as well as of numerous intrinsic neurons. The latter are particularly important because (1) they complicate the identification of nociceptors, particularly in the mucosa, and (2) they may contribute to the transduction of pain.

2.2. GI nociceptors

In respect of extrinsic afferents, the division of the autonomic nervous system into sympathetic and parasympathetic divisions is a misnomer that only accurately refers to efferent functions [27]. Rather, the most useful broad anatomical and functional division is into that of vagal and spinal visceral afferent fibres [95,104]. The latter may be further divided into splanchnic and pelvic afferents, with these following the paths of sympathetic and parasympathetic nerves, respectively. Vagal and spinal nerves have endings in all layers of the gut wall (Fig. 1), which, unlike some somatic sensory nerve endings, lack defined anatomical specification such as encapsulation. Axons are in the most part unmyelinated (C fibres) with a minority having thin myelination (Aδ fibres). It is generally held that vagal afferents have a much lesser role in nociception than spinal afferents [58], however, the vagus may have some role in pathophysiologic conditions [95]. The reader is reminded that much of the following description relates to experimental animals.

2.3. Spinal GI nociception

Spinal visceral afferents represent 10–20% of nerve fibres in splanchnic nerves, and project to all layers of the gut wall including the serosa and mesenteric attachments where they terminate as bare nerve endings [36]. Combined tracer and electrophysiologic studies have placed these fibres as the main source of visceral nociception with single-unit recordings from various gut regions demonstrating that high-threshold fibres are almost exclusively of spinal origin [184]. In addition to mucosal endings [151], which may participate particularly in chemonociception, there are three further neurophysiologically defined groups of spinal mechanosensitive afferents: (1) *Tonic* (or wide dynamic range) mechanoreceptors which have tonic levels of resting activity and respond like vagal muscle afferents linearly with rising wall tension starting at low thresholds [224,225]. In addition to signalling sensations, such as fullness, these continue to be activated well into the noxious range and may thus act as mechanonociceptors. (2) *High threshold* (or phasic) mechanoreceptors have low resting activity and respond only to noxious intensities of organ distension and are thus considered mechanonociceptors [224,225]. Aside from innervating the gut wall, such afferents have many endings located at intensely mechanosensitive sites in the mesentery and serosa [45,235]. They are also chemosensitive, responding directly to a variety of inflammatory mediators [148] and may mediate well-characterised responses to ischaemia at sites near mesenteric vessels [45,147,175]. (3) *Silent* nociceptors, which only develop activity and mechanosensitivity after exposure to inflammatory mediators. They are assumed but not proven to play a role in the viscera similar to that observed in somatic pain [147].

Unlike autonomic efferents that synapse in coeliac, hypogastric plexuses, or sympathetic ganglia, first-order spinal afferents traverse paravertebral and prevertebral ganglia (although some give collateral branches to the ganglia that mediate local reflex changes including blood flow [114]) to synapse like somatic afferents in the dorsal horn with cell bodies in the dorsal root ganglia. The detailed central neuroanatomy of visceral afferents has been most extensively studied in rodents where these fibres constitute only 7–10% of all afferent inflow into the cord, but have a widespread distribution in laminae I, II, V and X [104,179]. Whilst the spinal levels of sympathetic preganglionic efferents are well established between T1 and L2, the levels of afferents are spread across a broad range of DRGs with peak distributions for different organs. As a result, a generalised, overlapping, and viscerotropic distribution of spinal afferent fibre cell bodies exists [24] between C1 (upper oesophagus) and S4 (rectum and bladder) (Fig. 2a). This and the relatively small proportion of cell bodies assigned to the viscera are factors that probably contribute to the poor localisation of visceral versus somatic pain [56,225]. The viscerosomatic convergence at the level of the dorsal horn of the spinal cord accounts for the referral experienced with visceral pain.

Second-order neurons project to the brain through the spinoreticular, spinomesencephalic, spinohypothalamic and spinothalamic tracts [9], all of which lie in the anterolateral quadrant of the spinal cord (Fig. 2b). Whilst the first three of these tracts mainly activate largely unconscious and/or automatic responses to visceral sensory input including alterations in emotion and behaviour, the latter transmits conscious sensation by its projection via sensory nuclei of the thalamus to the somatosensory cortex (SI/II lateral pain system), anterior cingulate cortex (ACC) (medial pain system) and the insula [9,10]. Whereas the main function of the lateral pain system is to provide intensity and localisation of the stimulus, the medial system modulates affective pain behaviour with stimulation of important autonomic and descending inhibitory pathways (see below). The insula and other regions such as the orbital prefrontal cortex have important roles in sensory integration and in the higher control of autonomic visceromotor and behavioural responses. This widespread distribution of afferent pathways to areas beyond those required for localisation alone may account for the strong emotional component of visceral pain (further discussed below) and differences between patients with chronic visceral pain and controls in the degree of activation of these pain areas [170,202]. A further visceral pain pathway has also been established in the dorsal columns of rats and primates [6,7,8] which passes via ipsilateral dorsal column nuclei [6] to the contralateral ventroposterolateral nucleus of the thalamus [6]. In humans, this pathway may also be important, although this is currently based on limited evidence [155].

The transmission of nociceptive information from visceral spinal afferents can be modulated in ways similar to that from somatic afferents with 'gating' influences from converging viscerosomatic nociceptive and non-nociceptive neurons. Pain thresholds in the viscera are increased by viscerosomatic inputs with transient

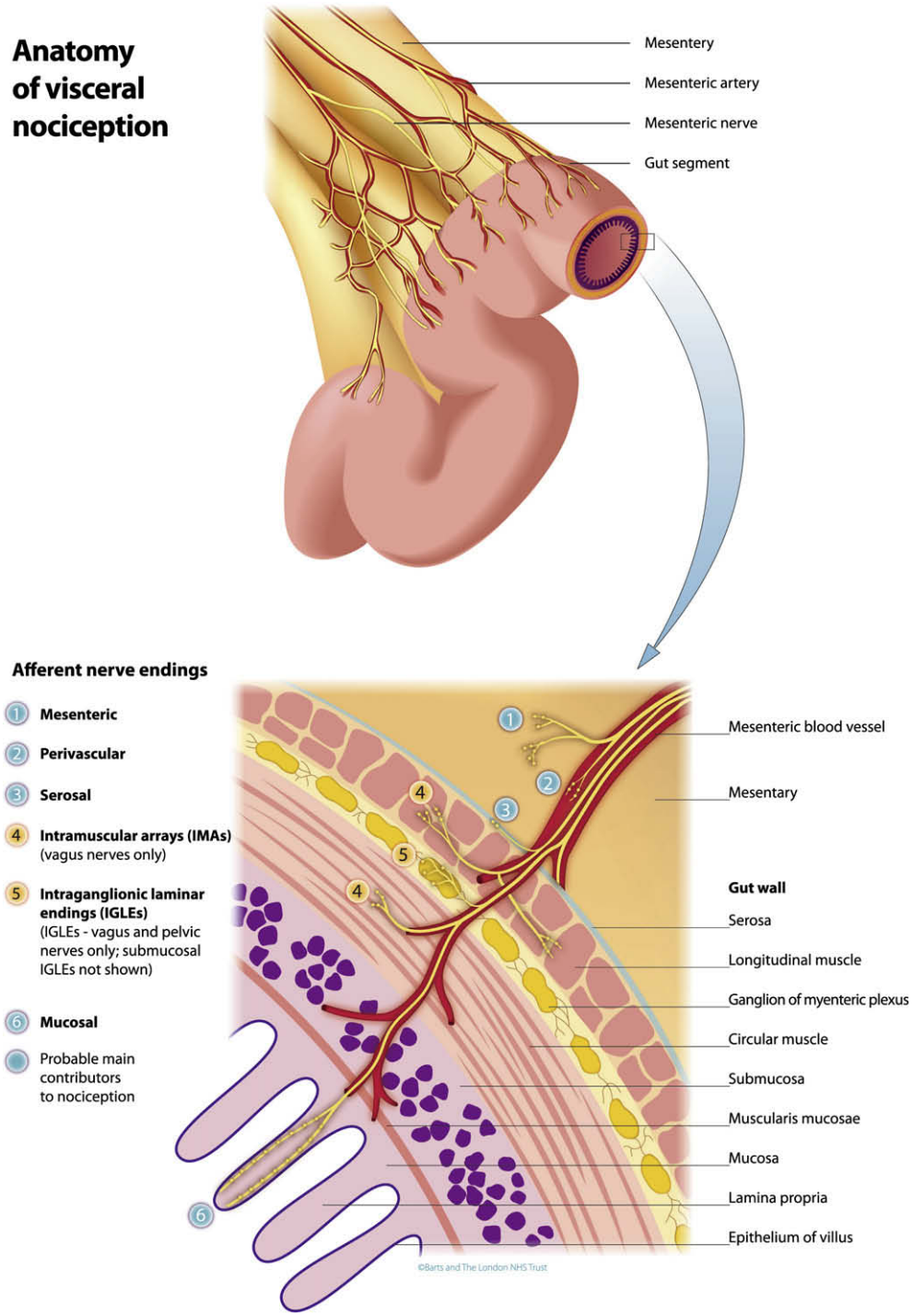

Fig. 1. Schematic representation of nerve endings in the gut wall. Endings are located in all gut layers, however, based on current evidence, those indicated are most likely to play a role in nociception with others, particularly those arising from vagal and pelvic nerves (intraganglionic laminar endings and intramuscular arrays) having no currently proven role.

inhibition of transmission demonstrated [236]. This may account for clinical phenomena such as the episodic nature of colic [10], the efficacious rubbing of 'a stitch', and the application of hot water bottles on the abdominal wall by patients (with subsequent *erythema ab igme*). Some neurons in the dorsal horn of the spinal cord are also strongly inhibited when a nociceptive stimulus is applied to any part of the body, distinct from their excitatory receptive fields. This neurophysiologic phenomenon [140] underlies the long-established clinical phenomenon of counter-irritation [216], in which application of an acute aversive stimulus provides temporary relief of chronic and recurrent pain [245]. Recent studies suggest that some patients with chronic abdominal pain demonstrate abnormal perceptual responses and brain activation patterns to rectal pain when it is associated with concomitant heterotopic stimulation using ice water immersion of the foot, which is known to activate this system [255,256]. In a feline model of visceral pain, such neurons can also refine ascending information to assist in injury localisation [88].

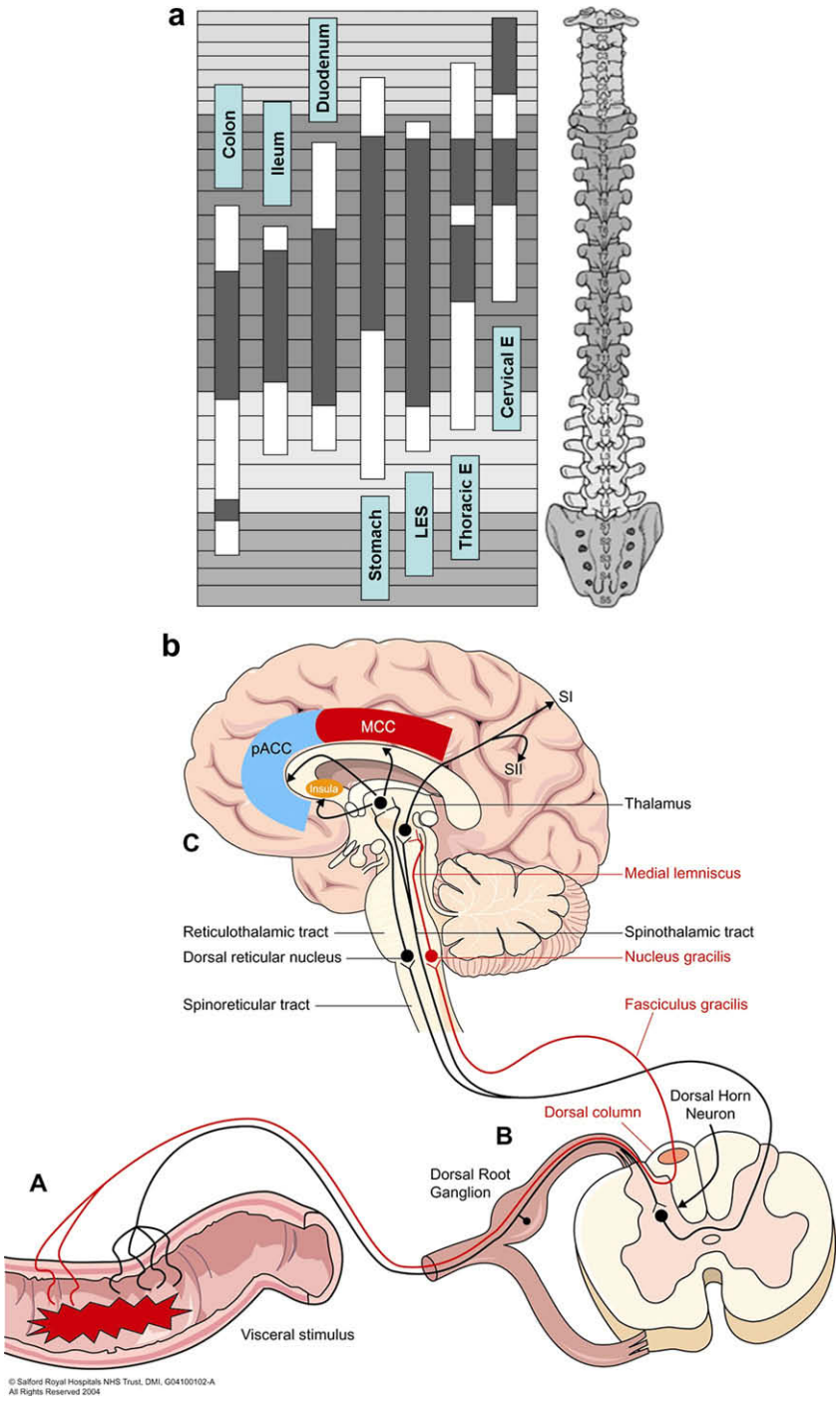

Fig. 2. (a) Schematic representation of the viscerotropic distribution of spinal afferent fibre innervation of the GI tract on the basis of retrograde tracer studies in experimental animals. The bars represent DRGs labelled with tracer from each organ with peak distributions (dark shade) and ranges (white) shown for each. Key: E, oesophagus. Note: although human studies suggest (like the bladder) a rectal afferent innervation to L5–S4, the anatomical lack of distinction of this organ from the colon in small mammals means that direct tracer data are unavailable. Adapted from Beyak et al. [24]. (b) Main central connections for GI pain pathways. Key: pACC, perigenual anterior cingulated cortex; MCC, mid-cingulate cortex. For clarity, spinomesencephalic and spinohypothalamic pathways have been omitted (reproduced with permission from Matthews and Aziz. Postgrad Med J 2005).

2.4. Pelvic nerves

Although grouped with spinal afferents, these neurons require special mention. Like the upper GI tract that has a dual innervation (vagal and spinal), the lower colon and rectum also receive an innervation that is anatomically independent of splanchnic neurons, but which similarly projects to the sacral spinal cord. Such pelvic nerves pass only through the pelvic plexuses and nerves, to segments S2–4 in humans (although this is species dependent L5–S5), with cell bodies in the DRGs at these levels. Approximately one-third of pelvic nerves are afferents [135], principally of the Aδ and C fibre types [90]. At a peripheral morphologic and functional level, these have more in common with vagal endings (below), being largely mechanosensitive [42,152] rather than nociceptive, and also have a population of intraganglionic laminar endings [152,183]. To what extent such endings participate in pain trans-

mission is currently not well studied but is of clinical importance in pelvic pain. The proximal extent of their influence as with motor nerves [128,219] is unclear and likely to be species dependent [60].

2.5. The role of the vagus in nociception

Approximately 50,000 (98% unmyelinated) vagal afferents supply the GIT [225]. Single-unit recordings in experimental animals demonstrate that unlike spinal afferents, the vagus consists almost entirely of low-threshold fibres [184], and conventional wisdom has thus placed the vagus as a sensor of primarily physiologic non-noxious stimuli (satiety, nausea, fullness, etc.). This is supported by vagal ablation studies, where levels of activity in the noxious distension range remain unchanged [211], by early human studies [252], and by clinical observations relating to the affects of vagal stimulation [223]. Outside the physiological range, studies have, however, demonstrated that noxious gastric distension is associated with continued firing of a subgroup of low-activation threshold neurons termed 'wide dynamic sensitivity' afferents [185]. In relation to specific types of vagal nerve endings, mucosal receptors have rapidly adapting neurophysiological responses to fine stroking and do not respond to distension [105,187,189] and at basal conditions are thus unlikely to have a significant mechanonociceptive role. Chemosensitivity to a wide range of intraluminal chemical and osmotic stimuli is their main role, as well as mediation of some unpleasant sensations such as nausea and vomiting [25,27], with their further activation by inflammatory mediators implicating them as 'silent' chemonociceptors in disease states [142,233]. Two further specialised groups of endings terminate deeper in the bowel wall. The first group, intramuscular arrays, consists of two or more parallel processes originating from a single axon [26] and is unlikely to have major roles in nociception, responding to low levels of distension or contraction of the gut wall with a slowly adapting, linear relationship to wall tension within the physiological range [37]. The second group, intraganglionic laminar endings (IGLEs) [180], terminates as a cluster of multiple endings which encapsulate a myenteric ganglion. A combination of fast axonal labelling techniques with electrophysiological characterisation has shown that these act as mechanosensors in response to low intensity shearing forces between circular and longitudinal muscle [152,269] but have no established role in nociception. Whilst they clearly (by close apposition) also have potential to respond to intraganglionic release of mediators by intrinsic neurons termed recently as 'intrinsic–extrinsic 'crosstalk' (below) [35], a true 'sensory' role for this interaction requires further proof.

Vagal afferents have their cell bodies in the inferior vagal ganglion in humans, and mainly in nodose ganglion in animals, thence projecting centrally to the brainstem where their processes terminate in the nucleus of the tractus solitarii. These neurons in turn project to the thalamus (mostly via the parabrachial nucleus) and thereafter to specific areas of the cortex sometimes described as the 'visceral sensory neuromatrix [10]'. In addition, vagal afferents project directly to other areas such as the hypothalamus, amygdala, peri-aquaductal grey (PAG) and locus coeruleus (LC) regulating emotional, autonomic and behavioural responses.

2.6. The role of the enteric nervous system in nociception

It is clear that neurons intrinsic to the gut wall cannot convey conscious sensation and strictly speaking therefore should not be termed 'sensory'. Nevertheless, of the now 16 functionally defined classes (in the guinea pig at least) of neurons whose cell bodies are intrinsic to the gut wall, approximately 20% of the half billion neurons present participate in the afferent limb of local reflexes including peristalsis in response to chemical and mechanical stimuli [93]. To avoid confusion, these are now described as intrinsic primary afferent neurons (IPANs) [126] rather than as intrinsic 'sensory' neurons [136]. Morphologically, IPANs have a Dogiel type II appearance [93] with multiple dendrites and a single axon, and demonstrate characteristic 'after hyperpolarisation' neurophysiological properties caused by three inward somal currents. These include a tetrodotoxin (TTX)-insensitive Na^+ current consistent with the proven expression of the nociceptive ion channel $Na_v1.9$ [207]. Indeed, it is now well established that IPANs can be damage sensing and respond to noxious luminal conditions by mediating powerful local reflexes to expel organisms/toxic chemicals from the GI tract [4]. This finding is also in keeping with their binding of the nociceptor-associated plant lectin IB4 [111]. Whether such neurons, half of which project to the myenteric plexus of their own and adjacent ganglia [92], can participate in signalling to extrinsic afferents (perhaps by interactions with IGLEs) and thence conscious pain, remains an attractive but yet unproven hypothesis [35]; and one that may prove difficult to establish. Their role in peripheral sensitisation is discussed below.

2.7. Summary box

- Current information suggests that GI nociception is mediated almost entirely by spinal visceral afferents.
- A combination of chemo- and mechano-nociceptors, especially spinal mesenteric and serosal nerve endings, mediates acute pain as occurs with significant distension or ischaemia. Mucosal endings probably have a greater role after sensitisation such as occurs in inflammatory states.
- The roles of the vagus and intrinsic afferents either alone or in combination in pain transmission, especially that from the mucosa, are receiving increasing attention.

3. The molecular basis of gastrointestinal pain

It has been noted that spinal visceral afferents particularly those arising from the mesentery are the main source of GI nociception. There is no particular reason to suppose that such neurons differ greatly from their somatic counterparts, having similar ontogeny (although less studied) and basic morphology (bare nerve endings, unmyelinated or thinly myelinated axon, pseudo-unipolar with cell bodies in the DRG and first synapse in the dorsal horn). In terms of mechanisms of pain transmission, it is therefore not unreasonable to consider the evidence for similar molecular events in visceral nociception. The main experimental methods used to determine these events are in general limited to inflammatory pain and are listed in Table 1.

3.1. Peripheral visceral sensory signalling and sensitisation (Fig. 3)

The peripheral terminals of nociceptors confer much of their specialised properties. In common with other afferents, generator potentials are produced by opening voltage-gated sodium channels in response to a depolarising stimulus, and are terminated by a combination of time, voltage-gated inactivation of these channels and opening of a voltage-sensitive outward potassium conductance [100]. In somatic afferents, $Na_v1.7$ carries much of the TTX-S (sensitive) current and appears to be the critical switch for mechanonociception [176]. This appears to also hold true for visceral afferents with similar TTX-S currents recorded from DRG and nodose ganglia of experimental animals following retrograde axonal labelling from various GI organs [34,229,232]. TTX-R (resistant) currents are localised preferentially to small, unmyelinated

Table 1
Experimental methods used in determining molecular mechanisms of visceral nociception.

- Studies on isolated (cultured) cells (*in vitro*) (Ca^{2+} imaging, patch clamping and intracellular recordings)
- Electrophysiologic studies of afferent nerve fibres ± sensitisation
- Studies of provoked rodent pseudo-affective behaviours and visceromotor responses following chemical or microbial-induced luminal inflammation and
  - Modulation of these responses by pharmacologic blockade (selective antagonists)/gene knock-out or knock-down using siRNA)
- Tissue (protein and RNA) expression studies of molecular targets (following sacrifice: gut, DRG, nodose, spinal cord)
- Studies of protein expression in full-thickness GI tissues from patients with proven inflammatory pain conditions, e.g. inflammatory bowel disease
- Studies of human healthy volunteers exposed to intraluminal inflammatory stimuli with subsequent specific pharmacologic manipulation

nociceptor-like fibres with the predominant channels being $Na_v1.8$ and 1.9. Both have specialised biophysical properties that may complement each other's function, with $Na_v1.9$ influencing overall membrane excitability and possibly amplifying small stimuli [5,65]. $Na_v1.8$-like currents are present in most DRGs innervating the viscera [34,232], whereas $Na_v1.9$ is preferentially expressed in a subset of GDNF-sensitive, IB4-reactive small nociceptors that are less populous in visceral DRGs [204], but have been noted to also be expressed by intrinsic neurons [186,207] whose role in nociception remains to be established. The further relevance of sodium channels to visceral pain is illustrated by the observation that point mutations in the SCN9A gene (encoding $Na_v1.7$) lead to both somatic (primary erythermalgia) and visceral (familial rectal pain (FRP)) syndromes by increasing channel activity [208]. In terms of rectifying currents, both I_A (rapidly inactivating) and I_K (delayed rectifier) currents have been demonstrated in GI extrinsic sensory neurons, including stomach [67] and ileum [229]. A discussion of further currents, e.g. hyperpolarisation (I_H), and channels, e.g. calcium-activated potassium channels and voltage-gated calcium channels, can be found elsewhere [27].

Transduction of noxious GI stimuli into generator currents at a molecular level, in common with somatic nociceptors, requires the expression of ion channels that are able to respond with a high threshold to particular changes in the mechanical, chemical and thermal environment [197]. The identification of such transducers, starting with TRPV1 [53], over the past 10 years has been an area of major scientific progress and one that may eventually translate into therapy (below). Studies in heterologous expression systems and knock-out mice have led to an ever expanding list of non-selective cation, potassium and ligand-gated ion channels with functions in somatic pain [262]. In the GI tract, three groups have been well characterised: (1) Transient receptor potential (TRP) channels are a large family of highly conserved channels that subserve sensory functions as diverse as hearing and pain [197]. Several are known to be expressed by extrinsic spinal and vagal afferents as well as by intrinsic neurons throughout the GI tract of experimental animals [15,44,246] and man [161,268]. There is good experimental evidence to suggest that TRPV1, TRPV4, and recently TRPA1 have roles, to a varying degree, in GI chemo-, thermo- and mechano-nociception [32,44,53,72] and that TRPV4 may directly transduce mechanosensation [145]. With special reference to the GI tract, many of these channels also contribute to the 'tasting' of a variety of potentially noxious (this being itself a question of personal taste!) foodstuffs such as chilli, menthol, garlic, mustard, horseradish and some herbs [23,53,153,265]. (2) Acid-sensing ion channels (ASIC 1–3) are members of a voltage-insensitive, amiloride-sensitive epithelial Na^+ channel/degenerin family of cation channels [244] that are sensitive to pH ranges 6–7 and are, with albeit some conflicting evidence [77], considered to have direct roles singly or as a 'transduction complex' in GI mechanosensation [188] as well as in chemonociception from luminal acid [127]. And (3) $P2_X$ purinoceptors ($P2_X1$–9) are ligand-gated membrane cation channels that open following ATP binding [48]. They thus have a role in transduction of chemical stimuli, which is increased at reduced extracellular pH [181], as well as contributing to mechanosensation [264].

3.2. Peripheral sensitisation

Peripheral sensitisation represents a form of stimulus-evoked nociceptor plasticity in which more prolonged stimulation, particularly in the context of injury or inflammation, leads to a change in the chemical milieu that permits nociceptor firing at lower thresholds than that required for an acute noxious stimulus, leading to the phenomenon of decreased pain thresholds at the site of injury (primary hyperalgesia). There is abundant experimental and clinical evidence to suggest that this occurs in the inflamed GI tract (oesophagus to colon) with several studies directly demonstrating electrophysiologic endpoints, i.e. increases in TTX-R and TTX-S currents and reductions in restorative potassium currents resulting in changes favouring nociceptor excitability [28,33,34,67,229]. Such sensitisers include kinins, e.g. bradykinin; biogenic amines, e.g. histamine and 5HT; prostanoids, e.g. PGE_2 growth factors (NGF and GDNF); proteases; chemokines and cytokines as well as reductions in pH and increases in ATP [10,104]. Whilst some nociceptor sensitisers can mediate their effects directly by altering receptor kinetics of VGSCs, e.g. PGE_2 [101], and cation channels, e.g. low pH and ATP [117], the majority of the effects are induced by binding to a number of specific G-protein coupled receptors (GPCRs) on the nociceptor membrane with subsequent activation of multiple intracellular signalling pathways including protein, PI3 and MAP kinases (reviewed: [262]). Such signalling mechanisms thence have the secondary effect of reducing transduction thresholds of cation channels, e.g. TRP channels, usually by phosphorylation [31]. In keeping with a role in GI nociception, expression of all relevant GPCRs, e.g. Bradykinin 2 (B2) receptors [43], PG receptors [159], histamine receptors [212], 5HT receptors [96], TrK A [73], Ret [84] and PAR_2 [55] receptors, has been demonstrated in several classes of GI afferents with a further subset of GPCRs having actions that modulate sensitisation by inhibition, e.g. somatostatin [206], some opioids [190] and CB1 receptors [124], with possible relevance to therapy.

Sensitisation can be further augmented by a number of interactions with adjacent cells including epithelia and inflammatory cells. Multi- (at least tri-) directional interactions with mast cells and lymphocytes underlie processes such as neurogenic inflammation in which biogenic amines stimulate the release of neuropeptides, such as substance P (SP) and calcitonin gene-related peptide (CGRP), with these then stimulating NGF release from several target cell types [143]. NGF, in addition to several other inflammatory mediators described (in the somatic nervous system), can promote a phenotypic switch to further sensitisation by retrograde signalling to the nociceptor soma and thence up-regulation (by a number of transcriptional mechanisms) of neuropeptide and particularly cation, e.g. TRPV [267] and VGSC [86], expression. The subsequent transport of such proteins (or very possibly transcripts) to peripheral and also central terminals permits a more prolonged peripheral and centrally sensitised phenotype,

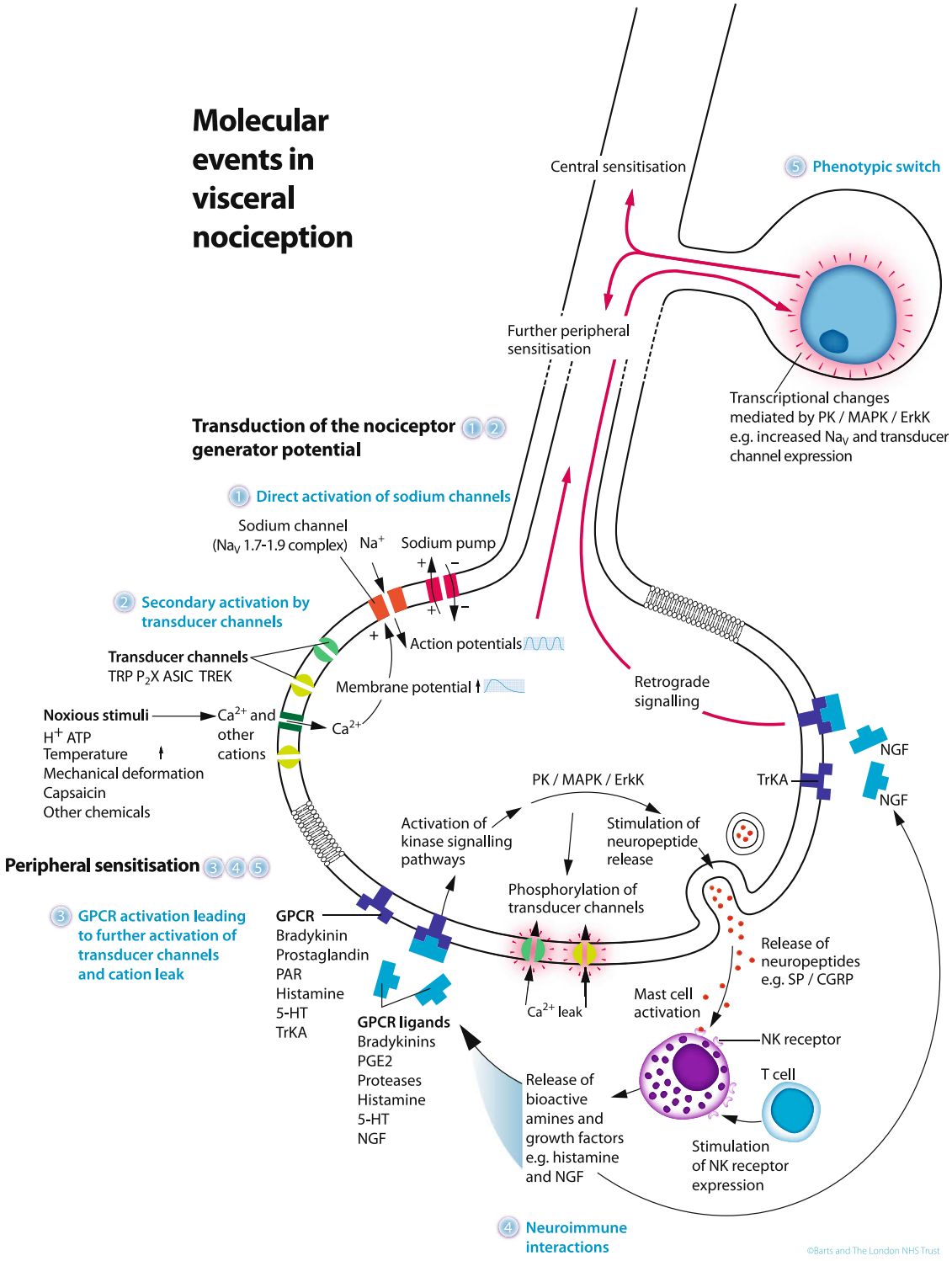

Fig. 3. Molecular basis of peripheral visceral nociceptive signalling before (1 and 2) and after (3–5) sensitisation. The main as yet proven steps in this process are schematically demonstrated (see text for details).

respectively. Increases in peripheral expression of transducer channels are now well documented in human end-organ studies in overtly inflammatory GI diseases [73,161,268] as well as in conditions characterised by PS in the absence of inflammation [3,30,59]. Although such changes have by necessity been observed in intrinsic neurons or small nerve endings (by limitation of availability of human DRG or spinal cord tissues), experimental studies support these observations. Considering gastroesophageal reflux disease as an example (a condition in which PS has been clearly demonstrated [127]), and increased TRPV1 correlated with

sensitivity [30,161], TRPV1 is upregulated in response to acid exposure in DRG and nodose in a rat chronic reflux model [16] with TRPV1 antagonists ameliorating ulceration in the model [270]. Numerous comparable studies exist for colonic inflammation [68,173,261].

3.3. GI-specific sensitisation mechanisms

Of specific relevance to the gut is the additional presence of intrinsic enteric sensory neurons as well as other specific cell types such as enteroendocrine cells. It is eminently feasible that numerous (approximately 100 million intrinsic versus 100,000 extrinsic) afferents that are well known to express both SP and CGRP [93], whilst not directly being able to transmit conscious pain, can nevertheless participate by releasing these neuropeptides in response to noxious stimuli (via expressed transducer channels outlined above) and thus promote neurogenic inflammation. It may thus be that the above studies examining increases in intrinsic neuronal expression of such molecules or indeed mucosal endings might be observing an indirect but important part of the process of GI sensitisation. In addition to the release of biogenic amines from mast cells, enteroendocrine cells are also (unlike nearly all neurons) distributed in the epithelium itself and have the capacity to directly 'taste' the lumen. These cells are closely apposed to nerves supplying in the lamina propria and are able to basolaterally release substances such as 5HT – 98% of 5HT is in the GI tract [96], whose role in PS as well as in motor dysfunction is well established experimentally and in human conditions characterised by visceral hypersensitivity (VH) (see below). Very recent data suggest that mucosal epithelial cells may also participate in PS in certain contexts such as acid exposure with effects also in part mediated by TRPV1 [150].

3.4. Central sensory signalling and sensitisation

The central terminals of nociceptors drive synaptic input to second-order neurons, transferring information about site, duration and intensity of the noxious stimulus. In the somatic nervous system, it has been established that unlike low-threshold fibres that use glutamate as their sole transmitter, nociceptors use both this and a variety of neuropeptides, e.g. SP and 5HT, and trophic factors, e.g. BDNF, as transmitters and synaptic modulators [262]. There is reasonable evidence that GI nociceptors have a similar molecular identity with experimental studies demonstrating that NK [138], NMDA [132,192], AMPA [192] and 5HT [96] receptors present on the post-synaptic membrane have a role in visceral pain transmission. In terms of pre-synaptic release of transmitters in response to incoming action potentials, there is evolving evidence in the somatic nervous system that voltage-gated calcium channels ($Ca_v2.2$ and N-type) have a key role [262]. Such channels have not to our knowledge been studied in GI afferents, although a subunit (alpha2delta) of Ca_v receptors is evolving as an area of therapeutic interest (below).

3.5. Central sensitisation

Repetitive firing of action potentials from the periphery (as occurs with PS) leads to amplified responses to both noxious (hyperalgesia) and innocuous (allodynia) stimuli [10]. Such facilitation is triggered by greater pre-synaptic release of the above described transmitters, which, acting at their respective receptors, lead (much akin to PS) to increased intracellular calcium and calcium-dependent activation of protein kinases A and C [123]. This in turn leads to phosphorylation of N-methyl-D-aspartate (NMDA) receptors with a change in receptor kinetics that reduces their voltage-dependent magnesium block, thus increasing subsequent responsiveness to glutamate [263]. Central sensitisation also has

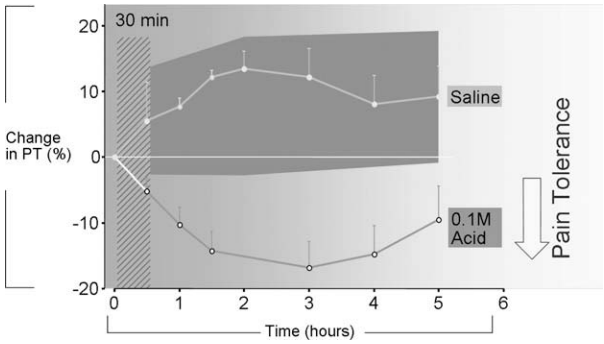

Fig. 4. Effects of distal oesophageal acidification on proximal oesophageal and chest wall pain thresholds to electrical stimulation. PT, pain threshold.

effects on adjacent spinal neurons leading to recruitment of previously 'silent nociceptors' and hypersensitivity in areas (somatic and visceral) that are remote from the site of peripheral sensitisation (termed secondary hyperalgesia). In the GI tract, viscerosomatic convergence has been shown experimentally in a number of gut regions and species, for instance, in the oesophagus of cats following sensitisation with acid [94]. The role of NMDA receptors in this process, like that in somatic pain transmission, has been confirmed experimentally [17,132].

Similarly, in humans, secondary hyperalgesia (by testing of the relevant dermatome) has been demonstrated in a number of conditions characterised by acute [228] and chronic abdominal pain [40,174,241]. In addition, viscerovisceral: proximal oesophagus and viscerosomatic: chest wall hyperalgesia has been demonstrated in a well-validated human volunteer model of distal oesophageal acidification (Fig. 4) [215]. This secondary hyperalgesia was both prevented and reversed with prostaglandin PGE2 [216] and N-methyl-D-aspartate (NMDA) receptor antagonists (ketamine) [258], suggesting that CS occurs by similar pathways to the somatic nervous system.

Balanced against these pro-nociceptive influences are the braking effects of endogenous opioids acting on mu and delta opioid receptors, GABA acting on $GABA_B$ receptors and endogenous cannibinoids acting on CB1 ± 2 receptors. In the peripheral somatic NS, these receptors are upregulated in response to central sensitisation [122]. Although this remains to be proven in the GI tract, there is sufficient experimental and clinical evidence to suggest that these receptors have similar roles in visceral pain modulation [200].

3.6. Summary box

- GI nociception is dependent on many of the peripheral and central molecular mechanisms observed in somatic nociception.
- Both peripheral sensitisation and central sensitisation have been demonstrated as mechanisms in visceral pain.
- The roles of several 'transducer' cation channels, e.g. TRPs and ASICs, are receiving particular attention because of their proven activation by chemical agents that are in some cases specific to the gut.

4. Modulatory influences on GI nociception

Whilst a body of work exists in somatic neuroscience to suggest that pain can be modulated by extra-nociceptive neuronal and non-neuronal influences, there is perhaps even greater evidence that such factors can influence visceral sensation. This observation is rightly based on human stress experiences that evoke expres-

sions in common parlance such as "I had a gut feeling" or "I had butterflies in my stomach". Such expressions are not unfounded, with good evidence that both acute stress and state psychologic factors, such as affective co-morbidities, have important roles in chronic visceral as well as somatic pain conditions [12,107,251]. The link between negative emotion and unpleasant visceral sensations has been well demonstrated experimentally in humans. For instance, anxiety, when induced by mental stress, has been shown to increase the sensation of intestinal gas and increase pain during sigmoid colon distension [87]. In addition to increasing pain perception, anxiety induction has also been shown to increase unpleasantness ratings to painful stimuli [250]. This latter effect may be related to increased activity in the brain areas discussed that are known to be associated with the affective-motivational component of pain processing. In the oesophagus, non-painful sensation is experienced as more unpleasant during a negative emotional context in comparison to a neutral emotional context, with a positive correlation between intensity of the negative emotional context and the degree of insula and anterior cingulate cortex activity observed using functional magnetic resonance imaging (fMRI) [193]. Other studies have also shown anxiety induction to be associated with activity in the inferior frontal and temporal pole regions of the brain [125]. Given the importance of the vagus in sensory feedback from the gut as well as its integration with the limbic and paralimbic brain areas involved in homeostatic regulation including pain modulation, it is not surprising that visceral sensory experience is closely linked with emotional state. Functional brain imaging studies have suggested differences between somatic and visceral pain in "limbic cortex" activation underlying the greater unpleasantness of visceral pain [230,231]. Recently, however, when unpleasantness was controlled for, some of these differences were less evident [82].

An organism's response to a stressor is generated by a network of integrative brain structures, in particular subregions of the hypothalamus (paraventricular nucleus, PVN), amygdala, and PAG. As already noted, these structures receive input from visceral and somatic afferents and from cortical structures, such as the medial prefrontal cortex (PFC), and subregions of the ACC and insula [14,217,243]. This network provides outputs to the pituitary and pontomedullary nuclei (such as the locus coeruleus, LC, and raphe nuclei), which in turn mediate the neuroendocrine and autonomic output to the body, respectively [14,217]. This central stress circuitry is under feedback control via ascending monoaminergic projections from these brain stem nuclei, in particular serotonergic (raphe nuclei) and noradrenergic (including LC) nuclei, and via circulating glucocorticoids, which exert an inhibitory control via central glucocorticoid receptors located in the medial PFC and hippocampus. This complex network of brain structures modulates stress responses through an effector system referred to as the 'emotional motor system', the main output components of which are descending spinal pathways, the ANS, and hypothalamo–pituitary axis (HPA) [167] (Fig. 5).

4.1. Descending spinal pathways

Descending pathways from supraspinal centres can inhibit or facilitate depending on the nature of visceral stimulus [209,218]. At a cortical level, the ACC is the most important source of

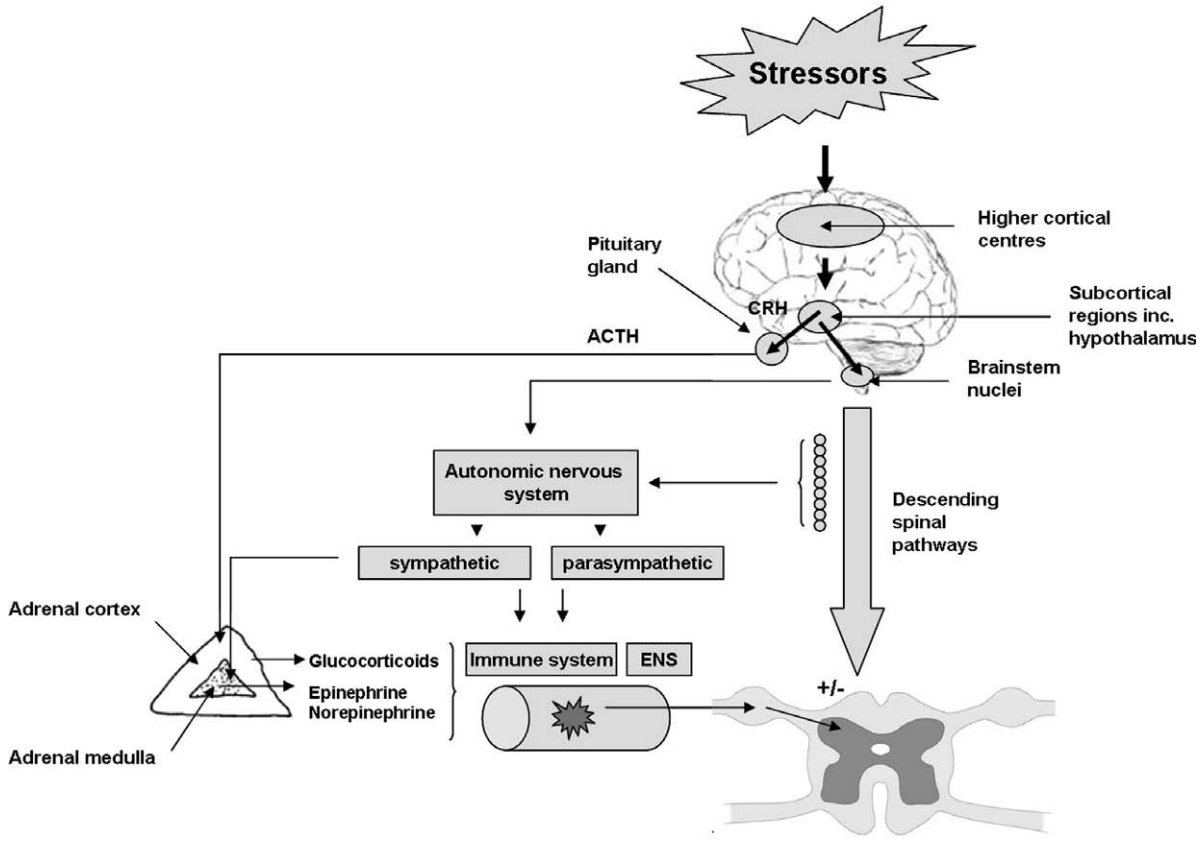

Fig. 5. Highly schematic representation of effector pathways from higher cortical centres in response to external stressors. Following activation of cortical and subcortical regions, such as the medial prefrontal cortex, subregions of the anterior cingulate cortex, insula and the hypothalamus release increased quantities of corticotropin-releasing hormone (CRH) inducing the release of adrenocorticotropin (ACTH) from the anterior pituitary. This in turn stimulates the release of glucocorticoids from cells in the zona fasciculata and reticularis of the adrenal glands. In response to ANS activation, cells of the adrenal medulla produce catecholamines such as adrenaline and noradrenaline, and both effector arms have potential to modulate enteric neuronal and gut immunocyte activity.

descending modulation, projecting to the amygdala and periaqueductal grey (PAG) of the mid-brain [10]. The PAG controls nociceptive transmission by means of connections through neurons in the rostral ventromedial medulla and the dorsolateral pontine tegmentum. These two regions project through the spinal cord dorsolateral funiculus and selectively target the dorsal horn laminae that accommodate nociceptive relay neurons. This circuit can therefore selectively modulate nociceptive transmission by its anatomical proximity to primary afferent nociceptor terminals and dorsal horn neurons that respond to noxious stimulation. Stimulation of these sites inhibits responses of spinal neurons to noxious stimuli. In the lower brainstem, the noradrenergic locus cereleus, serotenergic raphe nuclei and the rostrolateral ventral medulla receive inputs from the amygdala and PAG, and in turn project to the dorsal horn of the spinal cord where incoming transmission can thence be 'gated' [10]. While much of this information has been translated from somatic pain studies [199], a limited number of studies in experimental animals [57,97,172,178,271] and some human data [89] confirm that stimulating such areas can have analgesic effects by modulating visceral input.

4.2. The autonomic nervous system (ANS)

The ANS is a core part of the emotional motor system [113,165] and is a hierarchically controlled, bidirectional, body–brain interface that integrates afferent bodily inputs and central motor outputs for homeostatic-emotional processes [119]. This is particularly so for the viscera where, in addition to extrinsic nerves, the ENS has been considered by some to be a further effector of the ANS [24,118]. Animal studies suggest that differences in visceral and somatic ANS pain response are largely mediated via defence systems in which the roles of hypothalamus and PAG are best characterised. In particular, differential activation of either the ventrolateral or lateral PAG, arising in response to pain from deep/visceral or superficial structures, respectively, results in variation of patterned ANS defence responses and behaviours in animals (freeze versus fight-flight, respectively) [13]. Sympathetically mediated mechanisms are implicated in several chronic pain syndromes [102,221], and animal and human data support a vagally mediated inhibition of visceral nociceptive sensory inputs [75,198]. In this way, the ANS has the potential to modulate visceral sensory perception. Iovino et al. determined the effect of increasing sympathetic (and reducing parasympathetic) activity on the perception of intestinal stimulation. These autonomic modulations were induced using lower body negative pressure which induces venous pooling in the lower extremities [116]. Using brief distending stimuli in the intestine, the effect of lower body negative pressure on sympathetically mediated intestinal relaxation and on vagally mediated gastric relaxation was measured by corresponding barostats. The effect of lower body negative pressure on perception of duodenal distension was also compared to that on the perception of somatic stimulation. It was found that lower body negative pressure significantly heightened perception of intestinal distension without modifying perception of somatic stimuli. Also, the reflex responses to duodenal distension significantly increased both in the stomach and in the intestine. These findings support the reported nociceptive and anti-nociceptive actions of sympathetic and parasympathetic efferent systems, respectively.

The mechanism by which sympathetic and parasympathetic nervous systems modulate pain is unknown. The pro-nociceptive action of the sympathetic nervous system may relate to the release of catecholamines and/or prostaglandins from sympathetic nerve terminals in close proximity to the terminals of damaged primary afferent nerves. This in turn may result in the direct activation of afferent fibres that have developed (or upregulated) α-adrenergic receptors [118].

4.3. Hypothalamic–pituitary–adrenal axis

Animal studies have shown that responsiveness of these physiologic systems and the ability to adapt can be altered by adverse early life events, and that this seems to increase the organism's susceptibility to the negative effects of stress in later life. Al-Chaer et al. demonstrated chronic visceral pain hypersensitivity in adult rats that were subjected to either mechanical or chemical colonic irritation in neonatal life. Allodynia and hyperalgesia, the characteristics of central neuronal sensitisation, were present in the absence of any persisting peripheral pathology [7]. Early life events can permanently influence the development of central corticotropin-releasing hormone (CRH) systems, which, in turn, mediate the expression of behavioural/emotional, autonomic, and endocrine responses to stress. In rodent and non-human primate studies, maternal deprivation in infancy is associated with enhanced neural CRH gene expression and increased stress reactivity. In adulthood, these animals show greater activation of the HPA axis, sympatho-adrenomedullary systems, and central monoaminergic systems, and thus, greater vulnerability for stress-induced illness [63,169]. Although these studies are not specific to the GI tract, other animal studies have demonstrated that experimentally induced stress in rats alters gut motility in a pattern similar to that seen in humans, and can be both mimicked by intracerebroventricular or intravenous administration of CRH and blocked by a CRH antagonist, α-helical CRH [259]. Gue et al. reported that both stress and the administration of CRH (either centrally or intraperitoneally) enhanced the number of abdominal cramps evoked by rectal distension in a rat model without affecting rectal compliance, suggesting a role of CRH in visceral hypersensitivity (see below). These effects were also antagonised by α-helical CRH [106]. This study also demonstrated that peripheral administration of doxantrazole, a mast cell stabiliser, suppressed stress and CRH-induced rectal hyperalgesia to rectal distension [106]. It seems therefore that mast cell mediators are involved in the hypersensitivity response to rectal distension induced by stress. Previous studies have also highlighted the relationship between stress and colonic mast cell degranulation, and the fact that these effects can be reproduced by the administration of CRH [52], however, the mechanisms by which CRH modulates mast cell function are still unknown.

4.4. Summary box

- Emotional state has important modulatory influences on GI pain.
- Several cortical and subcortical brain regions process central responses to external stressors.
- Visceral perception and pain can thence be influenced by three main effector mechanisms: descending spinal pathways, the autonomic nervous system and the hypothalamo–pituitary axis.

5. Chronic unexplained gastrointestinal pain

5.1. Introduction

Abdominal pain is the commonest cause of presentation to a surgeon or gastroenterologist [226], with abdominal or pelvic viscera commonly implicated (by patient and/or physician), or proven to be the site of origin. Acute abdominal pain may be caused by several mechanisms with clinical presentation commonly reflecting the predominant underlying aetiology. Broadly, pain may arise as a result of visceral stretching as occurs with obstruction, inflammation as occurs in inflammatory bowel disease, or invasion/com-

Table 2

(a) VH: experimental studies

- Provoked rodent pseudo-affective behaviours and visceromotor responses following neonatal (e.g. maternal separation) [7,21,22] or acute stress (e.g. restraint, water deprivation, HPA activation) [1,41,52,106,139,259] and specific microbial-induced (e.g. *Trichinella spirilis* and *Nippostronylus brasiliensis*) [4,20,168] or chemical (non-inflammatory e.g. dilute acetic acid) [55,266] luminal sensitisation, with
  - Quantitative studies of immune cell activation, neuronal protein and gene expression following induction
  - Modulation of these responses by pharmacologic blockade (selective antagonists) or gene knock-out

(b) VH: clinical studies

- Increased sensitivity to intraluminal stimuli (mechanical, electrical, chemical, and thermal) [38,170,203,215,253] and to stimuli of relevant somatic referral area (indicative of CS) [40,174,195,215,241,255], and
  - Effect of state or provoked psychologic effects on these responses [79,85,107]
  - Modulation of these responses by pharmacologic therapy [see treatment section]
- Brain imaging studies (basal and with above stimuli) [166,170,202,242,256]
- Autonomic nervous system studies [2,247]
- Tissue studies on resected tissues or biopsies (mostly only mucosal biopsies) for immune activation [3,18,79,110] and nociceptor activation [3,54]

pression of nerves such as might occur in some cases of cancer. In a sense, acute pain, e.g. trauma/surgery, or that with a treatable cause, e.g. inflammation, is less problematic than chronic pain, particularly when this is not well explained. Highly relevant to the latter are two rather ill-defined and overlapping groups of conditions in which chronic GI symptoms, commonly including pain, cause considerable chronic morbidity. These in current parlance are the functional gastrointestinal disorders (FGID) [80] and gastrointestinal neuromuscular diseases [131]; terms that are at least partially dependent on method of classification, with the former being predominantly symptom-based and the latter measurement-based using a combination of clinical, physiologic [260], and, when available, histopathologic [130] criteria. Although the impact of visceral pain in general should not be underestimated, these conditions perhaps represent the greatest challenge to healthcare in Western societies and are discussed in further detail.

5.2. Functional gastrointestinal disorders: FGID

5.2.1. Clinical overview and importance

The term 'irritable bowel syndrome' is familiar now to most laity, and is one of an array of over 40 adult and paediatric disorders from mouth to anus classified (and reclassified) by a succession of committees from 1978 (Manning) onwards, with the latest being Rome III [7]. These systems have correctly moved away from reductionistic models of disease that had previously often led to inaccurate, demeaning and potentially harmful judgements being placed on patients without evident organic disease [80]. Using as a main basis the clustering of certain clinical observations with exclusion in some cases of an organic disease contribution, common diagnoses using this system include several pain-predominant conditions such as irritable bowel syndrome (IBS), functional dyspepsia, functional heartburn and functional abdominal pain syndrome. Pain is in fact the cardinal defining symptom of IBS [149]. These variably morbid conditions are now responsible for up to 40% of patients seen in secondary GI practice with considerable attendant health care costs. For instance, in 1998, a socioeconomic study demonstrated that the combined cost of healthcare utilisation and job absenteeism related to FGIDs was estimated to be $41 billion per annum in the eight leading western economies [91]. Given the lack of strongly effective therapies for pain in FGID [50], there are clinically unmet needs in this area.

5.2.2. Applied pathophysiology: visceral hypersensitivity

It is evident that in normal conditions, the gastrointestinal tract is 'conveniently' not a source of conscious sensory experiences over and above registration of physiologic sensations such as fullness and satiety. Thus, unpleasant sensations are generally only felt acutely or perceived as painful when stimuli exceed those in the physiological range. In this respect, colic occurs with supraphysiologic visceral distension with stimulation of spinal mesenteric (and possibly muscular) afferents, while ischaemic pain occurs when blood flow in the mesentery falls below acceptable physiologic levels. Such stimuli that permit beneficial cognition of potential tissue damage are rarely chronic with the exception of some cases of non-resolvable malignant obstruction or advanced mesenteric arterial disease, respectively. As noted earlier, however, many patients without such organic illnesses do complain, sometimes bitterly, of chronic abdominal symptoms, especially pain. Whilst it is possible that such pain could arise spontaneously in keeping with some somatic neuropathic conditions (below), there is much more evidence to suggest that in certain circumstances it becomes possible to sense stimuli that are normally non-noxious (analogous to allodynia) or increase afferent discharge to noxious stimuli (analogous to hyperalgesia). These nociceptive hyperalgesic phenomena, i.e. those occurring in response to a peripheral stimulus, are usually grouped together under the title of visceral hypersensitivity (VH). VH is present only to a varying degree in overtly inflammatory conditions [78,83,127], but is now firmly established as the pathophysiologic 'hallmark' of FGID [104,171].

In FGID, a plethora of studies have more than adequately demonstrated VH in most regions of the human GI tract (from oesophagus to rectum) [38,170,203,215,253]). For instance, in rectal distension studies of IBS alone there have been at least 20 studies since that of Ritchie et al. [203], and numerous reviews [10,11,104,127,164].

It is now generally held that there are four main co-operating mechanisms of VH:

- Sensitisation of afferent nerves (peripheral sensitisation).
- Sensitisation of spinal dorsal horn neurons (central sensitisation).
- Altered descending excitatory or inhibitory influences (neural and humoral).
- Misinterpretation of non-noxious sensation as noxious due to cognitive and emotional biasing.

It is clear that these mechanisms are at least in part encompassed within the discussion above of molecular events in GI nociception and modulatory influences thereof. However, further studies have attempted to address the contribution of these mechanisms more specifically to FGID and are summarised for brevity (Table 2), with accompanying key references provided for the reader.

Such interactions are best highlighted by considering the group (approximately 20%) of patients, who following a discrete

gastroenteritis episode have persistent symptoms including abdominal pain – a condition now known as post-infectious IBS [177]. The pivotal role of PS in this process is supported by studies demonstrating increased numbers and activity of mucosal pro-inflammatory cells, e.g. mast and enterochromaffin cells, as well as lymphocytes [18,79,110]. Although some contention exists regarding their exact functional role, such cells have been documented to be closely apposed to nerves supplying the intestinal mucosa, and to release a wide array of inflammatory mediators that can mediate PS [18,19,68]. Such changes can be replicated experimentally in rodents with discrete peripheral (luminal) non-inflammatory (infective or chemical) stimuli [4,18,20,55,266], and in humans can be demonstrated to lead to increased expression of molecules participating in peripheral nociceptor sensitisation, e.g. TRPV1 [3,59].

However, as already noted, cortical modulation is also important. In a prospective study of 94 patients with gastroenteritis, those developing post-infective IBS reported of more life events and had higher hypochondriasis scores than non-IBS-developing patients [107], with this evidence contributing to more general recognition that the potential to develop IBS can be influenced by the presence of negative affective states and personality traits [79]. Similarly, a very recent rectal distension study using fMRI demonstrated that IBS patients with a history of abuse report of more pain, greater MCC/PCC activation, and reduced activity of a region implicated in pain inhibition and arousal (sACC) [202]. Such studies thus emphasise the importance of external stressors, cognitive and emotional biasing as well as peripheral injury in GI pain. In respect of descending modulatory pathways, studies of CRH receptor antagonists in FGID patients (below) further affirm the strong modulatory role of the HPA axis in gut sensorimotor function and the possibility that derangements of its normal function occur in patients with FGID. Similarly, autonomic alterations such as low basal cardiac vagal tone have special relevance to pain sensitivity and have been observed in patients with IBS [2,247].

5.3. Gastrointestinal neuromuscular disease (GINMD)

5.3.1. Clinical overview and importance

It is well acknowledged even by steadfast Rome protagonists that a subgroup of patients with severe unexplained abdominal symptoms have demonstrable underlying abnormalities affecting the functional syncytium of differing cell types (intrinsic and extrinsic nerves, smooth muscle, interstitial cells of Cajal (pacemakers of gut motility and regulators of neuronal input to smooth muscle cells)) responsible for normal GI sensorimotor function. These disorders may be due to relatively rare congenital defects, for example, Hirschsprung disease, where the pathophysiologies are to some extent elucidated [109], however, most GINMDs are acquired in later life where their aetiology may be unknown (primary or idiopathic) or associated with another established disease (secondary), e.g. paraneoplasia, connective tissue disorders. Common to most GINMD are symptoms of impaired motor activity which manifest as slowed or obstructed transit [260] with or without evidence of transient or persistent radiologic visceral dilatation [158,227]; thus diagnosis (and classification), in the absence of histologic proof of neuropathy, myopathy or mesenchymopathy, is usually made using specialist GI physiologic measurements [260]. Primary diagnoses on this basis include enteric dysmotility, intestinal pseudo-obstruction and slow-transit constipation, all of which are characterised by abdominal pain [130,227,239]. Whilst perhaps the "tip of the iceberg" of unexplained gut dysfunction, these conditions result in considerable individual morbidity and incident mortality from a variety of sequelae including intestinal failure and suicide, sometimes as a result of unmanageable abdominal pain [130,227].

5.3.2. Applied pathophysiology: neuropathic pain

Although there is undoubtedly clinical overlap, the mechanisms underlying pain in GINMD may significantly differ from those in FGID. In the established taxonomy of somatic pain research, VH must be regarded as a form of nociceptive hyperalgesia, i.e. requiring peripheral stimulation. Despite the reporting of post-prandial pain in some patients, there is surprisingly little physiologic evidence that VH is an important mechanism in GINMD. Indeed, most studies attest to a reduction in visceral sensation on direct stimulation. For instance, although patients with slow-transit constipation (chronic intractable and unexplained constipation) almost universally complain of abdominal pain [129], several studies demonstrate rectal hyposensation [98,129] rather than hypersensitivity using the same stimulation paradigms used in IBS [170,253].

The nociceptor is designed to initiate activity only in response to noxious stimuli at its peripheral terminal. Thus, action potentials originating in the cell body or axon must be considered pathologically ectopic. In rodent nerve injury models of somatic pain, ectopic activity occurs not only in response to changes in ion channel expression in injured fibres [66,146], but also because of the signals delivered to intact fibres from other cell types such as glia and schwann cells that cause spontaneous firing [76,220]. The possibility that neuropathic mechanisms may contribute to the severe pain seen in GINMD is supported by the following observations: (1) the pain is often severe and unresponsive to standard analgesic therapies; (2) the pain is often not related to intraluminal stimulation, although it may be worsened in some; (3) there is good evidence for enteric neuropathy (degeneration and/or loss of neurons) in these disorders [83,130,133,239,249], as well as for the two other histopathologic components of the three described in neuropathic pain [220] – reactive gliosis [83,249] and perineural immune cells [130,239]; and (4) the pain cannot simply be the result of distension since most, particularly adult, patients do not have radiologic evidence of distension [130]; indeed those with constant intraluminal dilatation and significant abdominal distension as a result of myopthy do not always complain of pain (the main problem being one of vomiting and malnutrition) [158].

Surprisingly, despite the vast body of work examining neuropathic pain mechanisms in somatic research [66,262], and some suggestion that it has a role in chronic pancreatitis [74], this hypothesis has to our knowledge not been considered in GI pain studies. A paucity of studies have, however, examined the effects of pelvic denervation in animal models as a surrogate for physiologic disturbances in humans following hysterectomy and childbirth [53]. Pelvic denervation in rats causes not only reduced thresholds to colonic distension but also some spontaneous activity [64,232]. In humans, extrinsic denervation, suggested to occur after hysterectomy, leads to physiologic evidence of desensitisation [128,129], yet such patients frequently complain of abdominal and pelvic pain [29]. Although this argument potentially neglects confounders such as false attribution, altered pelvic anatomy, defeminisation, and the effect of constipation (a frequent accompaniment) [29,128], the possibility that spontaneous firing of afferents at a peripheral or central level might contribute to pain in GINMD as in somatic pain is an under-explored area.

5.4. Summary box

- Unexplained abdominal pain represents a significant healthcare burden.
- Visceral hypersensitivity is regarded as the pathognomonic feature of functional gastrointestinal disease (FGID) and has several well-established peripherally and centrally co-operating mechanisms.

- Neuropathic pain is a possible, yet underexplored mechanism, particularly in GI neuromuscular disease (GINMD).

6. Treatment of chronic gastrointestinal pain

6.1. Anatomically-based treatments

The anatomical basis for GI pain has been discussed. One approach to treating intractable pain of GI origin might thus be interruption of these pathways. Nerve blocks are well established in somatic, particularly radicular, pain from the spine. In chronic GI pain, their role has largely been limited to one of the adjuvant therapies (in addition to opioid analgesics) in palliation from inoperable advanced retroperitoneal (usually pancreatic) or pelvic malignancy [201]. Such pain may arise as a result of (1) direct tumour involvement of nerves, e.g. pelvic/sacral afferents, or of the viscus itself leading to obstruction or ischaemia, or (2) be associated with treatment, e.g. radiation neuritis, drug-induced neuropathy/constipation, or surgical denervation (discussed above). Invasive therapies are in general reserved for patients in whom pharmacologic and other non-invasive therapies are ineffective [117], and include a variety of nerve blocks that may be diagnostic (to determine origin of pain), temporarily therapeutic or as a guide to permanent intervention and its side effects, e.g. neurolytic blocks/surgical division [201]. Very recent advances such as endoscopic ultrasound-guided celiac axis block are also being made [144]. On this basis, approximately 50–80% of pelvic cancer pain patients benefit from nerve blocks [191,205] usually using (after previous test injection) intrathecal injection of phenol or alcohol to destroy nerve roots. Sympathetic blockade from the pelvis requires interruption of spinal afferents following the sympathetic innervation, usually by CT-guided needle neurolytic infiltration of the superior hypogastric plexus [194]. Sacral surgical rhizotomy, although sometimes effective [214], has largely been abandoned for benign and malignant deep pelvic/perineal pain not least because of profound subsequent bladder and bowel dysfunction [128]. More pertinent to current practice is, however, the rapidly developing area of sacral nerve stimulation (SNS). SNS is fast becoming the first-line invasive therapy for faecal incontinence and constipation [99,156]. In respect of the latter, it has been noted that unlike other surgical treatments in which pain is usually unaffected (even when defaecation is improved), SNS has beneficial effects for pain in patients with severe constipation [99,158] and may emerge as a therapy for pelvic pain.

6.2. Pharmacologic modulation of GI pain

As for VH, there are several reviews of new and evolving pharmacologic therapies for FGID and particularly IBS [50,112,163]. Current management of pain in FGID involves the use of analgesics, antispasmodics or antidepressants which often produce counterproductive side effects such as constipation or nausea. Pharmaceutical companies have invested heavily in the last two decades to develop the 'magic bullet' for managing pain in FGID. However, their efforts have not met with success with nearly all now having withdrawn from financial investment in this area. Most drugs developed on the basis of promising preclinical studies have shown either no effect or only a modest effect in clinical trials [50]. Part of the problem is that FGIDs are diagnosed on the basis of symptom-based criteria and with considerable inter-individual differences in pathophysiology leading to heterogeneity in study populations and endpoints [163]. Furthermore, there is a lack of disease biomarkers and good models of disease that can be used to test the proof of mechanism for the drugs before large-scale clinical trials are performed. Nevertheless, 'evolving' compounds are discussed below using the broad divisions used previously in the review. In GINMD, there are almost no well-designed clinical trials.

6.3. Drugs acting predominantly on peripheral signalling and sensitisation

Many potential targets have been discussed with relevance to modulating the complex set of molecular events underlying peripheral nociceptive transmission and in particular PS. Compounds have been developed that target some of all the three groups of receptors involved in these processes: voltage-gated ion channels, ligand-gated cation channels and GPCRs, as well as those affecting the bidirectional interaction of these molecules with local pro-inflammatory and immune cells. The following descriptions are limited to drugs acting on neurons rather than modulating other immune interactions, e.g. probiotics.

6.3.1. Voltage-gated ion channel blockers

Such molecules have the potential to address the fundamentals of pain transduction. Allowing for toxicity and non-specificity, some anticonvulsant drugs, e.g. carbamazepine and lamotrigine, have been trialled in somatic neuropathic pain with limited efficacy (Cochrane review: [254]). Although still agents of interest in neuropathic and inflammatory pain [262], in the GI tract to our knowledge only topical rectal lidocaine has been used in patients with IBS-related pain [240], with a further more detailed trial completed but unpublished (Clin Trials ID: NCT00108446), and carbamazepine has been used in the rare familial rectal pain syndrome [208]. More selective sodium channel agents have yet to be developed. Mechanosensitive potassium channels have not been addressed as pharmacologic targets but are a subject of current interest.

6.3.2. Cation channel blockers

The potential to modify the responses of a variety of such channels has been explored in somatic pain, and less so in visceral pain. Compounds directed to TRP, ASIC and P2X channels although explored in preclinical settings have had only modest progress to clinical trials [234] with the only study registered for GI pain now terminated (GSK: NCT00461682: rectal pain in IBS). In general, such drugs must therefore be considered to be at an early stage of development. In respect of serotonin, several studies have examined the effect of $5HT_3$ antagonists as therapeutic agents in IBS. Drugs such as alosetron, cilansetron and ondansetron were developed focusing mainly on their inhibition of motor activity [49,71]), however, their effects on VH have also been studied where there is conflicting evidence regarding a true, as opposed to secondary (due to increased compliance), peripheral visceroanalgesic effect [46,70, reviewed: 162].

6.3.3. G-protein coupled receptors

Perhaps more so than the above groups of receptors, this class of receptor holds most promise in novel peripheral treatments of GI pain. Broadly speaking, drugs have been developed to modify the bidirectional interaction between pro-inflammatory molecules and their receptors on neurons, with some modifying release and others blocking effects. Current trials based on the experimental evidence presented above include drugs acting at further serotonergic targets, especially the $5HT_4$ receptor. As with $5HT_3$, this receptor has predominantly been explored as a target for modulation of motor function to increase transit in constipation using agonists, e.g. Tegaserod [121]. Whether such drugs can affect visceral sensitivity is controversial [46] with some animal [103] but limited human data [62]. Proteinase-activated receptor 2 (PAR_2) antagonists have the potential to modulate visceral pain by acting on a variety of cells including sensory afferent terminals, as well as by altering

paracellular permeability to mucosal inflammatory cells [1]. Other agents such as those acting at neurokinin [213], CCK [39] and prostaglandin receptors [216], despite having biologic rationale at peripheral as well as central levels, have failed to demonstrate sufficient efficacy [81,257]. Others such as bradykinin and histamine receptors have yet to be studied in human GI pain conditions.

6.4. Drugs acting predominantly on central signalling and sensitisation

Although not exclusively active centrally, a number of drugs have been developed that act either to block excitatory transmission or promote inhibition. In respect of the former, robust analgesic responses have been shown in response to u and kappa opiate analgesics in animal models [137], in healthy humans suffering gastric distension [61], and in patients with IBS using rectal sensitivity as a surrogate marker [69,70]. However, further development of drugs such as fetotozine in this context seems to be lacking with none currently listed on clinical trials.gov. Nevertheless, other recent studies demonstrate the efficacy of using specific partial opioid agonists/antagonists to counteract analgesic-related constipation [238,248]. Similarly, blockade of NMDA receptors has been shown to have clear analgesic benefits in GI pain in animal models [17,132] and as noted blocks CS in a model of human oesophageal sensitivity [258]. However, drugs such as ketamine are unlikely to gain widespread acceptance given their global anaesthetic effects.

Alpha2delta ligands such as gabapentin and its more potent successor pregabalin have proven efficacy in neuropathic pain by their action not as originally presumed by GABA interactions but by binding to the alpha2delta subunit of calcium channels at central nociceptor terminals [157]). Following successful GI preclinical studies [182], data have recently become available on their role in reducing VH in patients with IBS [115,141] with proof that they modify the gold standard physiologic endpoint of rectal pain thresholds to barostat distensions.

The somatostatin analogue, octreotide, modulates GI pain by its effect as an agonist at the inhibitory somatostatin-2 (SST-2) and possibly SST-5 receptor. Based on ample preclinical studies [206], several studies demonstrate efficacy against VH in IBS [108,222]. There has been a very recent demonstration that B3-adrenoreceptor agonists stimulate the release of somatostatin in colonic tissue as well as in a rodent model of visceral pain [54]. Such agonists are currently in clinical development (http://clinicaltrials.gov/show/NCT00394186 and NCT 00343486).

6.5. Drugs acting predominantly on modulatory pathways

Several other agents have potential to modify the established role of stress, cognitive and emotional functioning (including the effects of anxiety and depression) in FGID characterised by abdominal pain and VH. These include those acting on the HPA axis such as CRF antagonists for which compelling preclinical data show that CRF administration can enhance colorectal distension-induced visceral pain in rats [106], and that VH can be reduced by CRF antagonists [139,210]. Furthermore, a recent study has also demonstrated normalisation of the electroencephalogram power spectra evoked by colonic distention by peripheral administration of the CRH receptor antagonist [237]. Although well reviewed [160], these have only reached phase II in humans with IBS (GSK: GW876008: Clinical trials.gov identifier: NCT00385099). Drugs with actions that oppose the pro-nociceptive effects of increased sympathetic activity might also be particularly effective in visceral pain where as noted autonomic responsiveness may have a greater role than in somatic nociception. Alpha2 antagonists such as clonidine and yohimbine received some attention in respect of preclinical studies of rectal distension [154], but appear to have fallen from grace. Very recent data suggest that some parasympathetic agonists may also be effective [120]. Finally, antidepressants such as SSRIs have been demonstrated to reduce visceral sensitivity in two studies of IBS [134,196].

7. Conclusions

The GI tract is an important site of pain which may unfortunately be chronic and unexplained. The field of GI pain research is starting to produce results that although temporarily still behind those in somatic pain are nevertheless becoming subject to the same scientific rigour. Increased understanding of the detailed pathophysiology of important GI pain syndromes is permitting the development of novel drugs that may have more established clinical roles in the future.

Conflict of interest

None declared.

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